(a) contacting an acid sphingomyelinase-deficient cell with a test compound;

(b) exposing the cell to a chemotherapeutic agent for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity;

(c) exposing an acid sphingomyelinase-deficient cell, in the absence of the test compound, to the chemotherapeutic agent for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity; and

(d) monitoring the exposed cells of steps (b) and (c) for the presence of an apoptotic morphology,

such that if the cell from step (b) exhibits a more severe apoptotic morphology, than that of the cell from step (c) the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

2. (Amended) A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

(a) contacting an acid sphingomyelinase-deficient cell with a test compound;

(b) exposing the cell to a chemotherapeutic agent;

(c) exposing an acid sphingomyelinase-deficient cell, in the absence of the test compound, to the chemotherapeutic agent; and

(d) comparing the levels of sphingomyelin and ceramide present in the exposed cell of step (b) to the levels present in the exposed cell of step (c),

such that if the level of sphingomyelin in the cell of step (b) is less than that of the cell of step (c), or the level of ceramide in the cell of step (b) is greater than that of the cell in step (c), the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

5. (Amended) A method for identifying a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

(a) contacting a cell exhibiting acid sphingomyelinase activity with a test compound;

(b) exposing the cell to a chemotherapeutic agent;

(c) exposing a cell exhibiting acid sphingomyelinase activity to the chemotherapeutic agent, in the absence of the test compound; and

(d) comparing the levels of sphingomyelin and ceramide present in the exposed cell of step (b) to the levels present in the exposed cell of step (c),

such that if the level of sphingomyelin in the cell of step (b) is greater than that of the cell of step (c), or the level of ceramide in the cell of step (b) is less than that of the cell in step (c), the test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

10. (Amended) A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

(a) exposing acid sphingomyelinase-deficient cells, wherein the cells are part of cell lines or a genetically engineered nonhuman animal deficient for the acid sphingomyelinase gene, in the presence or the absence of a test compound, to a chemotherapeutic agent for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity; and

(b) monitoring the exposed cells of step (a) for the presence of an apoptotic morphology, such that if the cells treated with the test compound exhibit a more severe apoptotic morphology than that of the cells not treated with the test compound, the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

11. (Amended) A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

(a) exposing acid sphingomyelinase-deficient cells, wherein the cells are part of cell lines or a genetically engineered nonhuman animal

deficient for the acid sphingomyelinase gene, in the presence or the absence of a test compound, to a chemotherapeutic agent for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity; and

(b) comparing the levels of sphingomyelin and ceramide present in cells treated with test compound to cells untreated with the test compound, such that if the level of sphingomyelin in the cells treated with the test compound is less than that of cells not treated with the test compound, or the level of ceramide in cells treated with the test compound is greater than in cells not treated with the test compound, the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

12. (Amended) A method for identifying a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising,

(a) exposing transgenic cells, comprised of cells deficient in endogenous acid sphingomyelinase gene activity that contain a functional human acid sphingomyelinase gene capable of expressing functional human acid sphingomyelinase, to a chemotherapeutic agent in the presence or absence of a test compound; and

(b) comparing the levels of sphingomyelin and ceramide present in cells treated with test compound to cells not treated with the test compound, such that if the level of sphingomyelin in cells treated with the test compound is greater than in cells not treated with the test compound, or the level of ceramide in cells treated with the test compound is less than that of cells not treated with the test compound, the test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

13. (Amended) A method for identifying a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising,

(a) exposing cells, wherein the cells are genetically engineered cells that exhibit a greater level of acid sphingomyelinase activity than non-genetically engineered cells of the same type, to a chemotherapeutic agent in the presence or absence of a test compound; and

(b) comparing the levels of sphingomyelin and ceramide present in cells treated with the test compound to cells not treated with the test compound, such that if the level of sphingomyelin in cells treated with the test compound is greater than in cells not treated with the test compound, or the level of ceramide in cells treated with the test compound is less than that of cells not treated with test compound, the test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

REMARKS

Claims 1-3, 5, 7 and 9-13 were pending and under consideration in the September 10, 2002 Office Action. Claims 1, 2, 5 and 10-13 have been amended herein. Accordingly, after entry of the instant amendment, Claims 1-3, 5, 7 and 9-13 will be pending and under consideration. A marked-up version of the claims to show changes made by the current amendment is attached hereto as **Exhibit A**. A clean version of all pending claims as amended herein is attached hereto as **Exhibit B**.

THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-3, 5, 7 and 9-13 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly not conveying to the skilled artisan that the inventor had possession of the invention at the time the application was filed. Specifically, the Examiner alleges that Applicants did not have possession at the time of the invention of the claimed methods employing any chemotherapeutic stress stimulus. Applicants respectfully disagree and direct the Examiner's attention to Section 2163 of the Manual of Patent Examining Procedure, 8th edition, entitled "Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, 'Written Description' Requirement" (which incorporates the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement cited by the Examiner).